# Artificial Gene Regulatory Networks and Spatial Computation: A Case Study

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**Abstract**

This paper explores temporal and spatial dynamics of a population of Genetic Regulatory Networks (GRN). In order to so, a GRN model is spatially distributed to solve a multi-cellular Artificial Embryogeny problem, and Evolutionary Computation is used to optimize the developmental sequences. An in-depth analysis is provided and show that such a population of GRN display strong spatial synchronization as well as various kind of behavioral patterns, ranging from smooth diffusion to abrupt transition patterns.

## Introduction

Widely studied in Biology, Gene Regulatory Networks (GRN) have drawn in recent years a growing attention from the field of Artificial Life and Evolutionary Computation. Indeed, GRN are known to display rich dynamics and have been both experimentally studied through simplified models (Jakobi, 1995; Banzhaf, 2003) as well as applied to control optimization problems such as the well-known inverted pole balancing problem (Nicolau et al., 2010) and foraging agents (Joachimczak and Wróbel, 2010). In these recent works, evolving artificial GRN have always been shown to be competitive with the state-of-the-art neuro-evolution techniques, possibly because of rich internal dynamics. However, while temporal dynamics within a single GRN have already been studied Banzhaf (2003), the spatial dynamics resulting from coupling of several GRNs remains to be explored.

The core motivation in this paper is to describe and study such temporal *and* spatial dynamics of a population of GRN in the context of a spatial computation problem. The methodology followed relies on Evolutionary Computation to provide optimization tools so as to fine tune the GRN parameters and structure for solving a typical multi-cellular artificial embryogeny problem. In this setup, the GRNs act as a decision model that is spatially distributed over a set of *cells* that interact on a local basis such that the whole *organism* converges towards a global state that is the closest possible to a pre-defined target state (e.g. a particular pattern).

Rather than performance on target matching, we study the emerging spatial and temporal dynamics during the course of the developmental process from the initial state to the end of development. Experimental investigations show that gene expressions are indeed strongly synchronized among GRNs, and display several behavioral patterns from smooth diffusion to abrupt transitions.

In the following, a review of existing artificial GRN models is provided. Then, the GRN model originaly proposed by Banzhaf (2003) is introduced as well as the developmental model used in this study. The combination of both models is described, and experimental investigations are conducted on the spatial and temporal dynamics of GRN. The paper concludes with a discussion and sketches future directions.

## Background on artificial regulatory networks

Many current developmental models rely on an Artificial GRN to simulate cell differentiation. These systems are more or less inspired by gene regulation systems of living systems. In living systems, organisms' cells have several functions. They are described in the organism genome and their expressions are controlled by the regulatory network (Davidson, 2006). Cells use external signals from their environment to activate or inhibit the transcription of genes into mRNA (messenger RiboNucleic Acid), the copy of the daughter cell's DNA (DeoxyriboNucleic Acid). Cells collect external signals through protein sensors localized on the cell membrane. Then, gene expression within a cell determines its behavior.

Eggenberger (1997) was one of the first to use a regulatory network to generate a 3-D organisms able to move in its environment by modifying its morphology. Reil (1999) proposed a biologically plausible model, with a genome defined as a vector of numbers. In this model, each gene starts with a particular sequence (0101), named the "promoter". Then, a graph visualisation is used to observe gene activations and inhibitions over time with randomly generated networks. Observations revealed the existence of several patterns such as gene activation sequencing, chaotic expressions or cyclic expressions. The author also pointed out that the system was able to display pattern self-repairing after random genome deteriorations. Banzhaf (2003) also described an artificial

GRN model strongly inspired by real-world gene regulation. This model will be detailed in the next section.

Starting from these two seminal models, various extensions and variations have been explored, for addressing various concerns and applications. Several works addressed Artificial Embryogeny problems with models of GRN ranging from cellular automaton modeling (Chavoya and Duthen, 2008) to stripped-down version of GRN combined with complex developmental systems (Knabe et al., 2008; Joachimczak and Wróbel, 2008; Doursat, 2008). Some works have also addressed control problems: using GRN as a control function to map a virtual robot's sensory inputs to its motor actuator values. This has been applied in various setup, from foraging agents (Joachimczak and Wróbel, 2010) to pole balancing (Nicolau et al., 2010).

Few case studies have been done to explain how regulatory networks can solve these problems. Schramm et al. (2010) studies the impact of the evolutionary process on the network itself. Other papers of the literature such as Mjolsness et al. (1991) or Thomas et al. (1995) propose an analysis of the regulatory network dynamics in a biological point of view. However, few papers deal with the analysis of such dynamics on artificial regulatory networks, which could be usefull if we want to use effectively the computational abilities of these models. The aim of this paper is to show the gene expression temporal answer of a regulatory network to solve a spatial problem. For this purpose, we use Banzhaf's GRN (Banzhaf, 2003) and its extension to a computational model presented in (Nicolau et al., 2010). The next section describes this model.

## The gene regulatory network

### The model

In this work, we consider the artificial Gene Regulatory Network (GRN) introduced by Banzhaf (2003). In this model, the network is coded into the genome as a sequence of 32-bit strings (termed *sites*). Each gene in the genome is marked by a particular sequence named the "promoter". When a promoter is detected, the next five sites represent a gene sequence that codes for a protein to be produced. Each site codes for a different molecule of the protein. The concentration of this protein will determine the expression level of the corresponding gene.

To determine the protein's concentration and thus the gene expression level, two sites, coded upstream of the promoter, enhance and inhibit the protein production. The dynamics of enhancer signal $e_i$ and inhibiter signal $h_i$ of a protein $i$ are given by the following equations:

$$e_i = \frac{1}{N} \sum_{j=1}^{N} c_j \exp^{\beta(u_j^+ - u_{max}^+)} \quad (1)$$

$$h_i = \frac{1}{N} \sum_{j=1}^{N} c_j \exp^{\beta(u_j^- - u_{max}^-)} \quad (2)$$

where $N$ is the total number of proteins, $c_j$ is the concentration of the protein $j$, $\beta$ is a scaling factor, $u_j^+$ (resp. $u_j^-$) is the matching degree of the enhancer (resp. inhibiter) site with the protein $j$ and $u_{max}^+$ (resp. $u_{max}^-$) is maximum enhancer's (resp. inhibiter's) matching degree observed in the whole genome. The matching degree $u_j^+$ (resp. $u_j^-$) consists in counting the number of "1" resulting from the application of a XOR operation to the protein $j$ and the enhancer (resp. inhibiter) pattern. The exponential function increases the impact of high value of gene expression and filter low values.

Finally, the concentration of produced protein $p_i$ follows the differential equation $dc_i/dt = \delta(e_i - h_i)c_i - \Phi(1.0)$, where $\delta$ is a scaling factor and $\Phi(1.0)$ constrains the sum of all concentration equals to $1.0$.

### Extension to a computational model

Originally, Banzhaf's artificial GRN is limited to study internal network dynamics. In order to use this model as a control function, Nicolau et al. (2010) proposed an extension by adding inputs and outputs to the regulatory network. This extension is detailed in the following.

**Inputs** Input values are coded with integers that will correspond to existing proteins. These input proteins can be involved in the regulatory process in two different ways: with their signatures to be considered during the matching process (in equations of $e_i$ and $h_i$) or with their input value to modify the differential equation $dc_i/dt$ of protein concentrations. Here, the second solution has been chosen as it allows a better resolution with regard to a continuous domain of the problem addressed in this paper.

**Outputs** In order to produce outputs in the regulatory networks, genes are separated into classes: transcription factors *TF-genes* and product proteins *P-genes*. Whereas TF-genes play the roles of regulatory proteins as in the original Banzhaf's model, P-genes are only regulated but do not regulate other proteins: their expression levels provide the desired output signals. These two kinds of genes are identified by introducing two new promoters, whose signatures are chosen so that their probability of occurence is equivalent and their matching as low as possible.

In the following, the regulatory network is used to produce cell differentiation, expressed by a cell coloration, while the developmental model described in the next section is responsible for the generation of the shape.

## The developmental model

The Generative Developmental System (GDS) *Cell2Organ* is composed of three layers of simulation: a *chemical* layer,

a *hydrodynamic* layer and a *physical* layer. These three layers can be enabled or disabled according to the needs of the experimentation. In the scope of this work, only the chemical layer is considered and will be described. More details about the developmental model are given in (Cussat-Blanc et al., 2008, 2010b,a).

The environment, implemented as a 2-D toroidal grid, contains several kinds of substrates. They spread within the grid, minimizing the variation of substrate quantities between two neighboring points. These substrates can spread on the grid at different speeds. Substrates can interact together in order to simulate a simplified chemical reaction. Only cells can trigger substrate transformations and collect or consume the energy of the transformation.

Cells act in the environment. Each cell contains sensors and has different abilities (or actions). An action has a energetic cost for the cell that will trigger it. An action selection system allows the cell to select the best action to perform at any moment of the simulation. This system is based on a set of rules *precondition→action (priority)*. It uses data given by sensors to select the best action to perform.

*Division* is a particular action that can performed if three conditions are respected. First, the cell must have at least one free neighbor to create the new cell. Secondly, the cell must have enough vital energy to perform the division (this required level is defined *a priori*). Finally, during the environment modeling, additional conditions can be added. A new cell created after division is totally independent and interacts with the environment. During the division, the GRN is executed in order to determintate the cell's color according to the morphogen quantity observed by the cell.

This model has been applied to shape generation (assembly of cells) in (Cussat-Blanc et al., 2008): a simple control function is evolutionary optimized to control cells so that it is possible to produce target shapes at the level of the organism within an environment with pre-positionned morphogens. In the current work, the control function considered is the extended Banzhaf's GRN model, coupled with an Evolution Strategies optimizer. Coupling the two models (GRN and developmental) is described in the next section.

## Coupling of the GRN and the GDS

### Precomputation of the cell differentiation

Different morphogen gradients are added to position cells in the environment. These morphogens are dedicated to differentiation. The configuration of these gradients will be described precisely for each experiment.

The cell differentiation is represented in the developmental model by a cell coloration. The concentration in morphogens measured by the cell in the environment defines the inputs of the regulatory network. These concentration are scaled to the range $[0.0, 0.3]$ in order not to overload the production of other regulatory proteins (the sum of all concentrations is normalized in the range $[0.0, 1.0]$). To obtain the cell coloration, each cell executes the regulatory network during its division stage. Only one color can be expressed. Therefore, the maximum of the expression level of all genes is taken after a stabilization of the network (chosen empirically after 1000 time steps of the regulatory network evolution). This gene expression will finally give the cell color during the development of the organism.

Because the cell can be positioned in a coordinate system and the morphogen gradients are prepositioned, the differentiation mechanism can be precomputed before the development stage. In other words, the problem can be translated to the search of an integer matrix. Each value of the matrix corresponds to the color of the corresponding cell in the chemical environment (1 for white, 2 for red and 3 for blue). The same regulatory network is independently executed at each point of the matrix with the morphogen concentrations that corresponds in the chemical environment. The regulatory network is used to generate a differentiation matrix that correspond to the desired pattern (also translated to an integer matrix). The developmental model then determines cell coloration using this differentiation matrix during the organism growth. During temporal development, this matrix thus simplifies computation within the model as cell differentiation can be directly set at cell creation. This is justified in the present context as pre-computing morphogen diffusion is a sub-problem that may not be critical for studying the already rich GRN dynamics.

### Evolutionary algorithm

A classical (250+250) evolution strategy (ES) evolves a population of regulatory networks coded by the binary string previously presented. The (250+250) evolution strategy consists in producing 250 offsprings from 250 parents and chosing the 250 best genomes to form the next population. The fitness function that evaluates each genome consists of counting the number of cells that do not match the desire pattern (wrong cell coloration). The evolution strategy is launched for 100 generation to minimize the quadratic error. In the following, the error is computed as the difference for each pixels between the image generated by the organism (cell differentiation determines pixel color) and the target image.

Genome modifications are only regulated by a common bit-flip mutation operator. The mutation rate is set to 2% at the begining of the run and adapted by the 1/5 rule of evolution strategies (Rechenberg, 1994): (1) the mutation rate is doubled when the rate of successful mutation is higher than 20%; (2) the mutation rate is divided by two when the rate of successful mutation is lower than 20%; (3) the mutation rate is doubled when the number of gene mutations in the population is less than 250 by generation.

The regulatory network's genome is randomly initializated. It is then duplicated 9 times with a mutation rate of 2% in order to increase the appearance probability of reg-

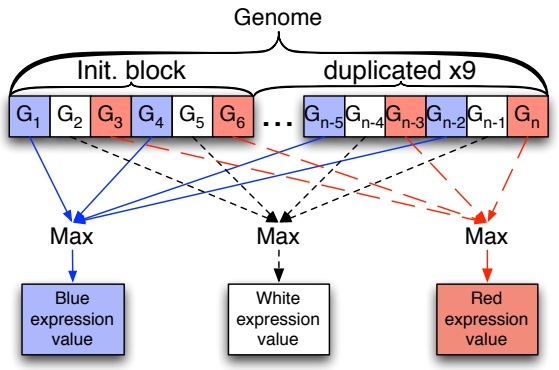



Figure 1: The genes of the genome are classified into three sub-parts: blue, white and red genes. The final expression value of each color is given by the highest value of the corresponding genes.

ulation sites. However, only three genes are necessary to code the thre needed colors (blue, white and red cell colors). The duplication of the genome implies a strong possibility to have more than the three needed genes coded in the genome. As described on figure 1, the genome is divided in three subpart. Each part codes for a specific color: blue, white and red. The highest gene expression value in one of the three sub-parts of the genome is taken as the expression value of the corresponding color.

Each differentiation matrix is developed only one time because the problem is deterministic. In other words, a regulatory network will always generate the same differentiation matrix and thus the same cellular pattern.

Figure 2 presents the convergence curves of the evolution strategy applied to our two problems of flag development presented in the next section. We can observe a stepwise evolution due to the only use of mutation. Moreover, even if the algorithm is set for 100 generations, it converges much faster (approx. 30 generations).

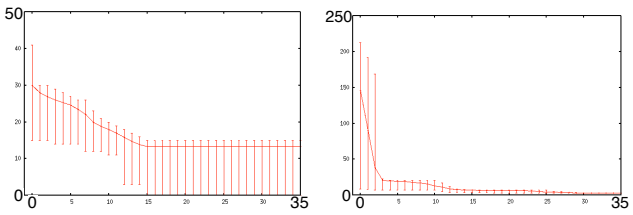



Figure 2: Convergence of the ES applied to a 45 cells French flag (left) and a 213 cell Japanese flag (right). X-axis represents the generation and the ordinate the min, mean and max fitness values (number of errors) for each generation.

# Experiments

## Benchmark: the French flag problem

In recent years, the French flag problem has become a classical benchmark for evolutionary computation. Introduced by Wolpert at the end of the 1960s (Wolpert, 1968), it consists in developing a French flag pattern starting from a single cell in the centre. This pattern is composed of three colored strips (blue, white and red). The French flag problem has various point of interests. In this paper, it is relevant as a spatial problem as it can highlight the differentiation capacities of a GRN-controlled developmental model: the color changes in the flag can easily be interpretated as a functional switch of the cell.

This benchmark has been addressed using various approaches. Lindenmayer (1971) used it to point out the capacity of his L-Systems to generate predefined shapes. Miller (2003) used a cartesian genetic programming approach and addressed self-repairing issues. Bowers (2005) used a embryogenic developmental model to produce a French flag. (Devert, 2009) addressed this problem with various methods based on using the NEAT neuro-evolution method (Stanley, 2004), Jaeger's Echo State Networks (Jaeger, 2001) and a reaction-diffusion model baring resemblance with the original Miller's model.

This benchmark became quite famous in the Artificial GRN community as it can be used it to show gene expressions of cells (Banzhaf, 2003; Knabe et al., 2008; Joachimczak and Wróbel, 2008). The major difference with previous work is that our contribution emphasizes the analysis on internal dynamics rather than focusing on pure performance and generalization. To this end, the problem is briefly described and experimental results are analysed, with a particular emphasis on internal dynamics of GRN as well as the spatial resolution of the problem in terms of gene expressions.

## Relationship between spatiality and temporality

Two different target shapes are considered: a French flag (three vertical strips) and a Japanese flag (white background with a red centered circle), each with its specific properties regarding the possible impact of morphogen gradients on the GRN expression levels.

**The French flag** In this problem, two morphogen gradients are positioned horizontally and vertically. They allow a precise positioning of the cells in the environment on the x-axis and y-axis. However, the target flag is developed in the diagonal of the environment. It implies an adaptation of the regulatory network to utilize both morphogens.

The regulatory network is trained on a 9x5 flag (45 cells). The target flag is composed of 3 strips of the same size: a blue in the bottom left of the environment, a white in the center and a red in the top right part. Figure 3 shows the obtained result. The resulting image perfectly matches with

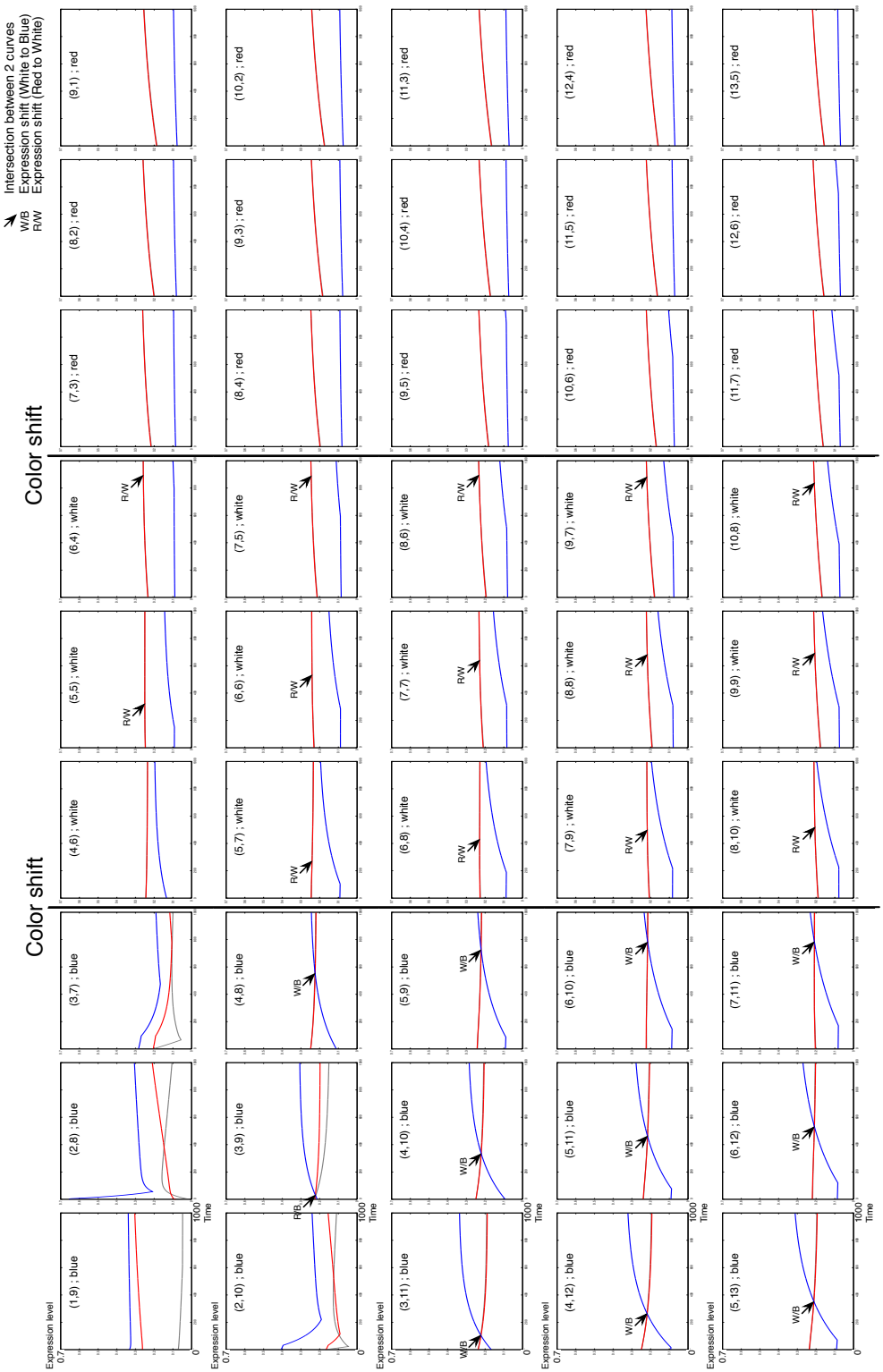



Figure 4: Variation of the gene expression levels over time for each cell of the organism. The curves correspond to the regulatory network activity of each cell of the French flag. The coordinate and the color of the cell are given by the title of each curve. We can observe a strong link between the delay of expression of appropriate gene and the distance to the color shift: the longer the distance to the color shift point, the faster the gene expression.

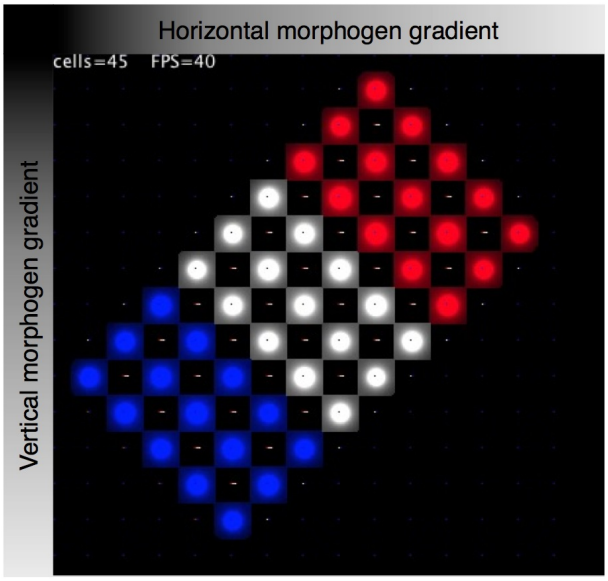



Figure 3: Development of the French flag

the target flag. To study the spatialization of the regulatory network, we extract all the curves of the color expression level over time of the regulatory network expressed in each 45 cell of the organism. These curves are presented in figure 4. The top left curve matches with the left corner blue cell of the organism in figure 3.

All these curves represent the variation of the three gene expression levels (blue, white and red) on the y-axis (scaled between 0 and 1) during the one thousand time steps of regulatory network's evolution. In the top left part of the figure, both morphogen orientations are represented according to the organism orientation.

It is interesting to notice the progressive softening of the blue curve in all curves and, at the opposite, the progressive increasing of the two other curves (red and white are almost overlapped). On the one hand, the transition between the blue curve and the white/red curves is very visible. On the other hand, the transition between white and red is hugely more smoothy. Both curves are very close all the time, except in the 5 top left curves. This exception is certainly due to a strong regulation shift in the regulatory network.

More relevant, the temporality of the color expression shifts is very observable. Considering only the blue and the white strips, the expression of the blue color is visible later and later in the regulatory network as the cell is closer to the white area.

The blue/white shift disappears from the curve when the cell must be white but we can assume by interpolation of the curves that the shift happens later. The same phenomenon is also present between the white and the red strips, as pointed out by the *R/W* black arrows. It exhibits the strong link between the temporality of the gene expression and the spatiality of the problem provided by the morphogen gradients.

Figure 5 presents the extraction of the regulatory network of the best evolved candidate. The nodes represent two groups of genes: the regulation genes named G1 to G39 and the product genes (that will produce the color of the cell) named P1 to P99. The size of each node is proportional to its number of links. The architecture of this network is interesting to observe. First, almost all the genes are used. Only two genes (G23 and G33) are not linked to the regulatory network. It shows the total use of the genome and the complexity of the network extracted. Secondly, six genes (G5, G14, G16, G27, G28 and G38) are interfacing the regulatory network and all product genes except P2, which is directly linked to the regulatory network. The interface has not been coded in the network. It only emerged thanks to the evolutionary process. Lastly, in the regulatory area, three genes (G4, G25 and G26) play a central role and they are strongly connected to the rest of the regulatory area. This regulatory area is very complex with a lot of links between all the nodes. This complexity is due to the necessity to exploit both gradients (horizontal and vertical).

**The Japanese flag** In order to investigate the independence of the coordinate system to the temporality answer of the regulatory network, development of a japanese flag in a radial coordinate system is studied. The goal is thus to develop into an image with a red circle in the center of a white 13x9 rectangular shape (a total of 213 cells). The same three genes have been kept in order to establish the capacity of the GRN to switch off a particular gene.

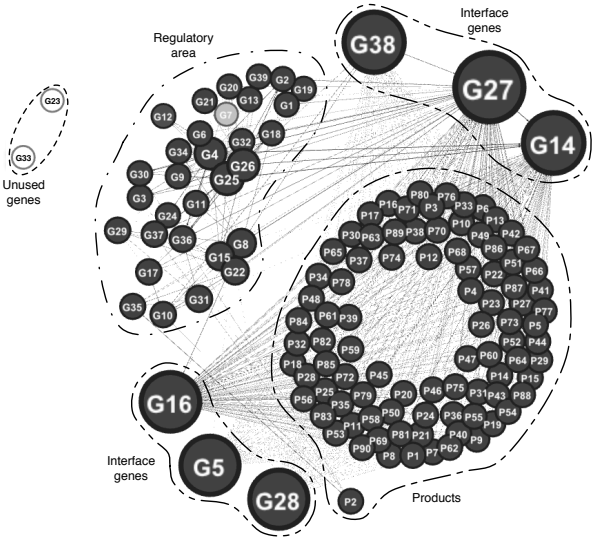
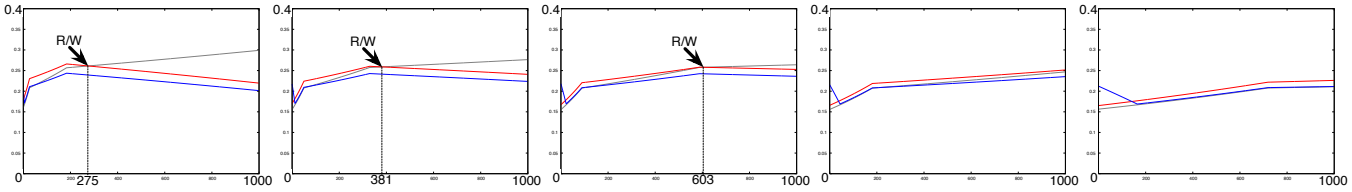



Figure 5: Gene regulatory network extracted from the best genome of the French flag with a threshold value of 19. G-genes represent regulation genes and P-genes represent the products of the regulatory network (a color expression).




(6,10), White (8,10), White (10,10), White (12,10), Red (14,10), Red

Figure 6: Gene expression level curves of 5 cells of the Japanese flag's central line. The curves' legends indicate the coordinate and the color of the cell that correspond to the gene expression.

As previously, only 15 generations is required to obtain a near-perfect flag (with only 3 pixels wrong). Figure 7 illustrates the flag obtained.

As for the previously presented French flag, all the curves of the gene regulation have been extracted in order to study the link between the temporality of the regulation and the spacialization of the problem. Figure 6 shows the curves of gene expression levels of five cells of central line: 3 whites cells and 2 red.

We can observe that all the expression levels are very close (y-axis is zoomed on the interval $[0, 0.4]$). The blue gene is also very strongly expressed even if not needed in this flag. Its inhibition by the regulatory network is correctly made but seems to be very weak. The same link between the temporality and the distance to the shift is also observable as on the French flag: the closer the colors shift, the later the gene expression levels shift. The same behavior is observable elsewhere on the flag and each transition stage can be obtained by rotation.

## Conclusions and Perspectives

The goal of this work was to investigate the use of Artificial GRN in the context of a spatial problem. We combined Banzhaf's GRN model to our own developmental model *Cell2Organ*, and experimental studies have been conducted on variations of the multi-cellular flag problem, a well-known benchmark in Artificial Embryogeny. Results from the experiments confirm the strong link between the temporality of the gene expressions in the regulatory network and spatial parameters of the problem. Indeed, change in the cell differentiation process among the organism is correlated by significant shifting in the GRN dynamics. The temporal aspect observed here also raises numerous question regarding the ability of a population of GRN to actually generate some desired behaviors. How many steps does it take to produce a correct output? What is the expressivity of such a system, in particular, how many basin of attractions can be encoded within one GRN template? Is it possible to have, depending on the context at hand, either a fast or a smooth shift between two regimes? These questions are of particular interest to explore further GRN-based control optimization problems (Joachimczak and Wróbel, 2010; Nicolau et al., 2010).

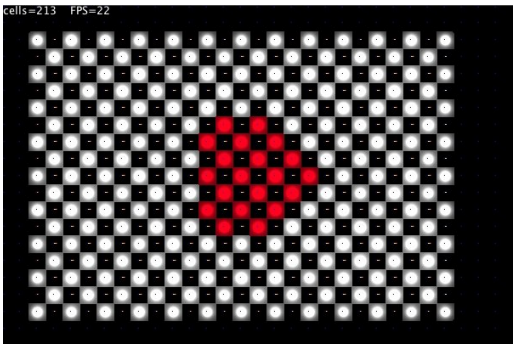



Figure 7: Development of a Japanese flag with a radial gradient.

The complexity of the regulatory network obtained was also somewhat surprising and raises the question as to the evolvability of such a representation. The regulatory network needed a large number of P-genes (not restrained in these experiments) in order to find a solution to the problem. This may be a symptom of code bloat, a well-known problem of uncontrolled growth in variable length representations and definitely requires further studies, with possible investigations with respect to penalizing bloat without undermining the model's performance.

Lastly, spatial problems addressed here are relevant for this kind of detailed study, but have limited applications in the current form. However, the field of applications is large and examples from Biology give a good indications on the variety of problems to be addressed: cell differentiation into neurones, development of muscular cell, tissues, etc. In the context of computer modelling, understanding the intrinsic properties of GRN may be relevant in a variety of problems requiring complex temporal and spatial interactions. Indeed, because of their structure, regulatory networks could be more suitable for continuous problems than other behavior controlers such as artificial neural networks or classifier systems.

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